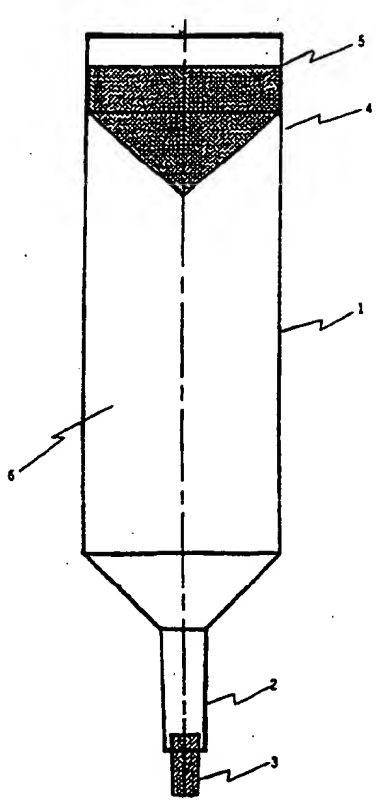


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(21) International Application Number: PCT/IB94/00327 (22) International Filing Date: 20 October 1994 (20.10.94) (30) Priority Data: 08/147,353 3 November 1993 (03.11.93) US (71) Applicant: BRACCO INTERNATIONAL B.V. [NL/NL]; De Boelelaan 7, NL-1083 Amsterdam (NL). (72) Inventors: HEFFERNAN, Gayle; 208 Vesper Avenue, Middlesex, NJ 08846 (US). WELSHER, Allen; 5 Packard Road, East Brunswick, NJ 08816 (US). (74) Agent: TOMOV GRISOGONO, Nenad; Bracco Research, 7, route de Drize, CH-1227 Carouge (CH).		(81) Designated States: AU, BG, CA, CN, CZ, FI, HU, JP, KR, KZ, NO, NZ, PL, RO, RU, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: METHOD FOR THE PREPARATION OF PRE-FILLED PLASTIC SYRINGES		
(57) Abstract <p>A novel method for the preparation of a pre-filled plastic syringe, and preferably the preparation of a plastic syringe pre-filled with a diagnostic contrast agent wherein said syringe comprises as components a barrel (1), a tip seal (3) capable of sealing the nozzle of the barrel and a piston (5) capable of sliding in the barrel and sealing the open end of the barrel opposite the nozzle, comprising the steps of: (a) providing at least one component of said syringe which is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and (b) filling and assembling said syringe.</p> 		

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METHOD FOR THE PREPARATION OF
PRE-FILLED PLASTIC SYRINGES

Field of the Invention

5 The present invention relates to a novel
method for the preparation of pre-filled plastic
syringes, and preferably to the preparation of
plastic syringes pre-filled with diagnostic
contrast agents.

10

Background of the Invention

Plastic syringes, pre-filled with liquid or
semi-solid materials suitable for diagnosis and/or
treatment of medical conditions, find utility in
15 the pharmaceutical arts. As can readily be
appreciated, it is desirable that such syringes
contain minimal amounts of pyrogens and viable and
non-viable particulates.

Methods for preparing pre-filled plastic
20 syringes have previously been disclosed. For
example, U.S. Patent No. 4,718,463 describes a
method for the preparation of pre-filled plastic
syringes comprising, among other steps, a step
wherein the barrel of the syringe is washed with a
25 multiplicity of jets of water to remove debris and
pyrogens from the barrel, followed by assembly and
filling of the syringe and a terminal autoclaving
step wherein the filled syringe and its contents
are sterilized.

Summary of the Invention

The present invention provides a method for the preparation of a pre-filled plastic syringe, comprising the steps of:

- (a) providing at least one component of said syringe which is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and
 - (b) filling and assembling said syringe.
- Preferably, the syringe comprises as components a barrel, a tip seal capable of sealing the nozzle of the barrel and a piston capable of sliding in the barrel and sealing the open end of the barrel opposite the nozzle, and further, said at least one component in step (a) includes one or more of the barrel, the tip seal and/or the piston. Most preferably, said at least one component in step (a) includes at least the barrel of the syringe. The present invention also provides a novel method for molding a syringe component, such as a barrel, tip seal or piston, comprising the step of molding said component under conditions which are substantially free of pyrogens and viable and non-viable particulates.

The method of the present invention, wherein at least one of the aforementioned components, preferably at least the barrel, is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates, allows the preparation of a pre-filled plastic syringe in a less cumbersome and more efficient manner than known methods by obviating the need for subsequent treatment steps such as water washing. Thus, while the component(s) molded under conditions which are substantially free of pyrogens and viable and non-viable particulates may optionally be treated

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subsequent to molding, such as by water washing, such subsequent steps may be omitted or reduced in intensity or duration by use of the present method.

Preferably, the component(s) molded under conditions which are substantially free of pyrogens and viable and non-viable particulates in accordance with step (a) are maintained under clean conditions until they are assembled in the syringe. In this regard, it is further preferred that clean conditions be maintained at least until the syringe is completely assembled (for example, that the partly assembled syringe be maintained under clean conditions). Thus, in a preferred embodiment, the present invention provides a method for the preparation of a pre-filled plastic syringe, wherein said syringe comprises the aforementioned barrel, tip seal and piston, comprising the steps of:

(a) (i) providing a barrel which is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates, and, optionally, providing a tip seal and/or a piston which is also molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and

(ii) maintaining said barrel and, optionally, said tip seal and/or piston, under clean conditions for use in step (b); and

(b) filling and assembling said syringe.

In a particularly preferred embodiment, the present invention provides a method for the preparation of a pre-filled plastic syringe, wherein said syringe comprises the aforementioned

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barrel, tip seal and piston, comprising the steps of:

- (a) (i) providing a barrel which is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates, and, optionally, providing a tip seal and/or a piston which is also molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and
- (ii) maintaining said barrel and, optionally, said tip seal and/or piston, under clean conditions for use in step (b); and
- (b) filling and assembling said syringe, wherein:
- (i) the tip seal is attached to the nozzle end of said barrel;
- (ii) the barrel and tip seal assembly is filled with a liquid or semi-solid through the open end of the barrel, said open end being opposite said nozzle end of the barrel; and
- (iii) the piston is assembled in said open end of the barrel; and
- (c) optionally, sterilizing the assembled syringe and its contents.

Brief Description of the Drawings

FIGURE 1 is a sectional view of a pre-filled plastic syringe prepared by the present method.

Detailed Description of the Invention

A preferred configuration of a pre-filled plastic syringe prepared by the present method is illustrated in FIGURE 1. As can be seen from FIGURE 1, the barrel 1 has a nozzle end 2, to which

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is attached a tip seal 3 and, at the opposite end 4, a plunger (or piston) 5. The piston may be depressed to express the liquid or semi-solid contents 6 of the syringe through the nozzle end.

5 According to the present method, at least one syringe component, preferably at least the barrel, is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates. The term "molded under
10 conditions which are substantially free of pyrogens and viable and non-viable particulates", as used herein, denotes molding under conditions meeting or exceeding Class 100,000 conditions with respect to particulates (Federal Standard No. 209E, "Airborne
15 Particulate Cleanliness Classes in Cleanrooms and Clean Zones, approved by the General Services Administration (Sept. 11, 1992), incorporated herein by reference), and, with respect to microbes, meeting or exceeding Class MCB-3
20 conditions (*Pharmacopeial Forum*, Volume 18, Number 5, pp. 4048 to 4054, In-Process Revision, The United States Pharmacopeial Convention, Inc. (Sept.-Oct. 1992), incorporated herein by reference), and, in addition, wherein the microbial
25 level of gram negative microorganisms is less than 1 cfu (colony forming unit) per cubic foot of air (and, preferably, also per 30 cm² of surface). Class MCB-3 conditions, and/or the aforementioned level of gram negative organisms, may be
30 maintained, for example, by sampling to determine the level of microbes present, and sanitizing or employing other control methods as required (e.g., by surface contact with alcohol, phenolic germicides such as "germ warfare", or chlorite

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salts such as sodium chlorite salts (e.g.,
"Expore")). As is understood by one of ordinary
skill in the art, "meeting or exceeding" denotes a
level of cleanliness which is equal to or greater
5 than the standard referred to.

With respect to particulates, the term
"molded under conditions which are substantially
free of pyrogens and viable and non-viable
particulates", as used herein, preferably denotes
10 molding under conditions meeting or exceeding Class
10,000 conditions (see the aforementioned Federal
Standard No. 209E); more preferably, conditions
meeting or exceeding Class 1,000 conditions (see
the aforementioned Federal Standard No. 209E); and
15 most preferably, under conditions meeting or
exceeding Class 100 conditions (see the
aforementioned Federal Standard No. 209E). With
respect to microbes, the term "molded under
conditions which are substantially free of pyrogens
20 and viable and non-viable particulates", as used
herein, preferably denotes molding under conditions
meeting or exceeding Class MCB-2 conditions (see
the aforementioned *Pharmacopeial Forum*); and more
preferably, conditions meeting or exceeding Class
25 MCB-1 conditions (see the aforementioned
Pharmacopeial Forum).

In addition to conducting the molding step
under conditions which are substantially free of
pyrogens and viable and non-viable particulates
30 (that is, under the classified conditions described
above), it is preferred to employ an elevated
temperature and/or pressure during molding, for
example, a temperature and/or pressure where
pyrogens, if present, may be partly or completely

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decomposed during molding. Also, if desired, the starting plastic material may be treated, for example, washed, such as with an aqueous (e.g., water for injection) or organic washing agent and/or sterilized, such as treated with ethylene oxide or irradiated, prior to molding.

Preferably, as indicated above, a component molded under conditions which are substantially free of pyrogens and viable and non-viable particulates is maintained under clean conditions prior to assembly into the syringe. "Clean conditions" include those defined above for conditions which are substantially free of pyrogens and viable and non-viable particulates, but may also include any art-recognized conditions for maintaining cleanliness such as enclosure in a sealed clean-room bag or wrapper for storage.

A syringe component molded under conditions according to step (a) of the method of the present invention may be provided which is substantially free of pyrogens and viable and non-viable particulates and which is suitable for assembly into a sterile syringe with minimal or no further treatment of the component prior to assembly. Thus, for example, a component such as the barrel molded under the conditions of step (a) of the present method may be assembled into the syringe without water washing. If desired, however, some further treatment may, optionally, be employed subsequent to molding.

In this regard, any of the components of the syringe, including those molded under the conditions of step (a) of the present method, as well as those molded under other conditions ("non-

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classified conditions"), may optionally be treated by one or more of the following steps subsequent to molding:

- 5 (1) blowing the component with a gas, especially with sterile filtered (e.g., filtered through a 0.2 μ m filter) and/or deionized (facilitating a decrease in the electrostatic attraction of particles to the molded component) air to remove particulate matter;
- 10 (2) lubricating the component, such as by treatment with a silicone lubricant;
- (3) washing the component with an inorganic (e.g., hydrogen peroxide or water) and/or organic (e.g., freon) washing agent, and,
- 15 optionally, rinsing the component, such as with water;
- (4) sterilizing the component, such as by contact with an antimicrobial agent (for example, hydrogen peroxide (e.g., in liquid or vapor form)
- 20 or ethylene oxide), by use of radiation (especially, gamma radiation), and/or by autoclaving (such as by use of steam at temperatures of 122 to 124°C and pressures of 33 to 35 psia); and/or
- 25 (5) preparing the component for storage or transport, such as by placing the component in a sealed, clean-room bag where it is not to be employed immediately after formation.

30 For those components molded under conditions which do not meet the conditions of step (a) of the present method, for example, Class 100,000 conditions where microbial monitoring is not employed or other clean room-type conditions not meeting the conditions of step (a), it is preferred

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that, at a minimum, a washing step, such as the above step (3) be employed.

Preferred Methods for Preparation of Barrel

5 The barrel of the syringe may be made of any suitable plastic, and is preferably made of polyolefin, including polyolefin polymers, copolymers and blends, especially polypropylene or blends thereof with polyethylene, or olefin
10 polymers and copolymers including methylpentene, or the like polyolefins.

 Preferably, the barrel is injection molded, such as by use of injection molding equipment under conditions known in the art for melting and forming
15 plastics (e.g., injection molding polypropylene pellets into syringe barrels by melting at 400 to 520°F (0.75 to 3 minutes) at 1000 to 1200 psi).

Preferred Methods for Preparation of Tip Seals

20 The tip seal of the syringe may be made of any suitable plastic, and is preferably made of flexible rubber elastomer such as natural rubber, butyl or halobutyl rubber or blends thereof. The tip seal may be molded, preferably injection or
25 compression molded, such as by use of injection or compression molding equipment under conditions known in the art. The equipment may, for example, be readily selected by one of ordinary skill in the art on the basis of the type of elastomer employed.

30

Preferred Methods for Preparation of Piston

 The piston may be any suitable type, such as a piston operable by a rod or handle for hand injection of the contents of the syringe or a

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piston operable by a power injector for mechanical injection of the contents of the syringe.

The piston may be made of one, two or more pieces. The piston may, for example, be a single
5 piece component, or a two-piece component consisting of a core and a flexible cover piece attached to or fitting over or onto the core (e.g., allowing the piston to seal the barrel of the syringe). In the latter case, the core is
10 preferably made of a relatively hard plastic such as a polyolefin (e.g., polypropylene) or polycarbonate, and the flexible cover piece is preferably made of a flexible rubber elastomer, such as those materials described above with
15 respect to the tip seal; the two pieces may be pre-assembled to form the piston prior to insertion into the barrel. Each of the separate pieces of the piston may be molded and optionally treated as described above.

20

Preferred Methods for Assembly of Syringe

In a preferred embodiment of the present method, the tip seal is assembled by attachment to the barrel, preferably automatically. Filling may
25 then be conducted, such as by use of automatic filling equipment. The syringe may be filled with any suitable liquid (e.g., solution or suspension) or semi-solid (e.g., paste, cream or ointment). Preferably, the syringe is filled with a liquid
30 diagnostic agent suitable for injection, for example, a contrast agent such as ProHance™ (gadoteridol) or Isovue® (iopamidol).

The liquid or semi-solid may then be sealed by insertion of the piston, optionally followed by

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a terminal sterilization step. When employed, sterilization is preferably achieved by steam autoclaving. Preferred temperatures for steam autoclaving are those from about 120 to 124°C; preferred pressures are those from about 44 to 53 psia. It is particularly preferred to select a pressure set point so that, under the conditions of the autoclaving, the pressure inside the syringe is approximately in equilibrium with the pressure outside the syringe in the autoclave. An overpressure (pressure outside syringe in autoclave exceeds that in syringe) or an underpressure (pressure in syringe exceeds that outside syringe in autoclave) may, however, also be employed.

In addition to the tip seal, barrel and piston, the syringe prepared by the present invention may include other components, such as any of those known in the art, for example, a handle or rod for the piston, a needle, a protective cap for the needle, and the like.

The following Example further illustrates the present invention, and is not intended to in any way limit the scope of the present claims.

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EXAMPLE 1PREPARATION OF PRE-FILLED
PLASTIC SYRINGES

5

In the following Example, wherever Class 100 conditions are employed, it is understood that the microbial level of gram negative microorganisms is less than 1 cfu (colony forming unit) per cubic
10 foot of air or per 30 cm² of surface, and that the conditions meet or exceed Class MCB-3 conditions.

Preparation of Syringe Components15 (i) Barrels

Polypropylene resin pellets, prepared by extrusion of a molten (450 to 520°F) polypropylene resin mix (suitable for formation of clear plastic barrels) into pellet form, are pneumatically loaded
20 into a hopper and fed into a sprew under Class 100,000 conditions. The pellets are then melted at 400 to 520°F for 0.75 to 3 minutes while under 1000 to 1200 psi (also under Class 100,000 conditions). (Methylpentene olefin resin pellets may
25 alternatively be employed, and are preferably dried at 160°F for 4 hours prior to being fed into the sprew.)

Under Class 100 conditions (for this and the following steps unless indicated otherwise), the
30 syringe barrels are formed by injection molding of the molten resin, and the formed barrels are picked robotically from the mold. The barrels are optionally blown with 0.2µm sterile filtered, deionized air and/or lubricated with silicone. The

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barrels are then presented by the robot for visual inspection. A Class 100 molded polycarbonate Luer nut may optionally be machine assembled at this time.

5 Still under Class 100 conditions, the barrels are matrixed (oriented) into a Class 100 molded polypropylene carrier holder, aligning the barrels for further processing. The barrels may optionally be placed in heat-sealed clean-room bags
10 when stored prior to use. The barrels may also optionally be sterilized, such as by contact with ethylene oxide or by autoclaving. When gas sterilization is contemplated, it is preferred to place the barrels in gas permeable heat-sealed
15 clean-room bags and to sterilize the barrels *in situ*.

(ii) Tip Seals

Halobutyl rubber is compression molded under
20 Class 100,000 conditions to produce flexible rubber tip seals. Under Class 100 conditions, the tip seals are washed with purified water, United States Pharmacopeia, XXII (1990) (hereinafter, "U.S.P., XXII") which is treated to be pyrogen free or,
25 preferably, water for injection, U.S.P., XXII, optionally siliconized, and optionally placed in heat-sealed clean-room bags when stored prior to use (gas permeable such bags may be employed when gas sterilization, such as by ethylene oxide or
30 autoclaving, *in situ* is desired (see the "Assembly and Fill" section below); such bags may be other than gas permeable if it desired to employ a method of sterilization such as irradiation).

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(iii) Pistons

Two-piece pistons are prepared by assembling, preferably mechanically, under Class 100 conditions, an inner hard plastic core and a flexible rubber cover. The pistons may optionally be placed in heat-sealed clean-room bags (preferably, gas permeable such bags when gas sterilization in situ is desired) when stored prior to use and/or sterilized, such as by gamma irradiation, or, preferably, by contact with ethylene oxide or by steam autoclaving.

Cores

The cores of the pistons are made from polypropylene (or, alternatively, polycarbonate) molded under the Class 100 conditions described above for molding the barrels. The cores may, alternatively, be molded under non-classified conditions and washed with water for injection U.S.P., XXII or purified water U.S.P., XXII which is treated to be pyrogen free. Optionally, the cores may be placed in heat-sealed clean-room bags (e.g., gas permeable for reasons described above) when stored prior to use.

Covers

The flexible rubber covers are molded under the conditions used to prepare the flexible rubber tip seals, and, under Class 100 conditions, are washed with water for injection U.S.P., XXII or purified water U.S.P., XXII which is treated to be pyrogen free, and siliconized. The flexible rubber covers may optionally be placed in heat-sealed clean-room bags (e.g., gas permeable for reasons described above) when stored prior to use.

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Assembly and Fill

5 The tip seals are sterilized, such as by contact with ethylene oxide or by irradiation or, preferably, by steam autoclaving, and, under Class 100 conditions, are placed into the hopper of a filling machine, and assembled to the barrels. Also under Class 100 conditions, liquid contrast agent, such as Isovue® or ProHance™, is filled into the barrel through the open piston end.

10 The two-piece pre-assembled pistons, placed into the filling machine hopper, are inserted into the barrels using a vacuum seating mechanism. The filled syringes are steam autoclaved at a temperature between 120 and 124°C and a pressure
15 between 44 and 53 psia. Following particulate inspection, the syringes are labeled and packaged for use.

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What is claimed is:

1. A method for the preparation of a pre-filled plastic syringe, comprising the steps
5 of:
 - (a) providing at least one component of said syringe which is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and
10 (b) filling and assembling said syringe.
2. The method of claim 1, wherein said syringe comprises as components a barrel, a tip seal capable of sealing the nozzle of the barrel
15 and a piston capable of sliding in the barrel and sealing the open end of the barrel opposite the nozzle, and further, wherein said at least one component in step (a) includes one or more of said barrel, said tip seal and/or said piston.
20
3. The method of claim 2, wherein said at least one component of step (a) includes said barrel.
- 25 4. The method of claim 3, comprising the steps of:
 - (a) (i) providing a barrel which is molded under conditions which are substantially free of pyrogens and viable and non-viable
30 particulates, and, optionally, providing a tip seal and/or a piston which is also molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and

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(ii) maintaining said barrel and, optionally, said tip seal and/or piston, under clean conditions for use in step (b); and
(b) filling and assembling said syringe.

5

5. The method of claim 4, wherein said step (b), and optionally the following step (c), comprise the steps of:

(b) (i) attaching the tip seal to
10 the nozzle end of said barrel;
(ii) filling the barrel and tip seal assembly with a liquid or semi-solid through the open end of the barrel, said open end being opposite said nozzle end of the barrel; and
15 (iii) assembling the piston in said open end of the barrel; and
(c) optionally, sterilizing the assembled syringe and its contents.

20 6. The method of claim 2, wherein said at least one component in step (a) is molded under conditions meeting or exceeding Class 10,000 conditions.

25 7. The method of claim 6, wherein said at least one component in step (a) is molded under conditions meeting or exceeding Class 1,000 conditions.

30 8. The method of claim 7, wherein said at least one component in step (a) is molded under conditions meeting or exceeding Class 100 conditions.

9. The method of claim 2, wherein said at least one component in step (a) is molded under conditions meeting or exceeding Class MCB-2 conditions.

5

10. The method of claim 9, wherein said at least one component in step (a) is molded under conditions meeting or exceeding Class MCB-1 conditions.

10

11. The method of claim 3, wherein a component of said syringe is treated by one or more of the following steps subsequent to molding:

- (1) blowing the component with a gas;
- 15 (2) lubricating the component;
- (3) washing the component with an inorganic and/or organic washing agent, and, optionally, rinsing the component;
- (4) sterilizing the component; and/or
- 20 (5) preparing the component for storage or transport.

12. The method of claim 11, wherein one or more component(s) of the syringe are not molded under conditions which are substantially free of pyrogens and viable and non-viable particulates in accordance with step (a) and are, prior to assembly into said syringe, washed with an inorganic or organic washing agent and optionally rinsed, and/or
25
30 sterilized.

13. The method of claim 12, wherein the one or more component(s) of the syringe which are molded under conditions which are substantially

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free of pyrogens and viable and non-viable
particulates in accordance with step (a) are, prior
to assembly into said syringe, not washed with an
inorganic or organic washing agent and/or are not
5 sterilized.

14. The method of claim 13, wherein said
barrel is not water washed subsequent to molding
and prior to assembly in said syringe.
10

15. A method for molding a syringe
component, comprising the step of molding said
component under conditions which are substantially
free of pyrogens and viable and non-viable
15 particulates.

16. The method of claim 15, wherein said
syringe component is a barrel, tip seal or piston.

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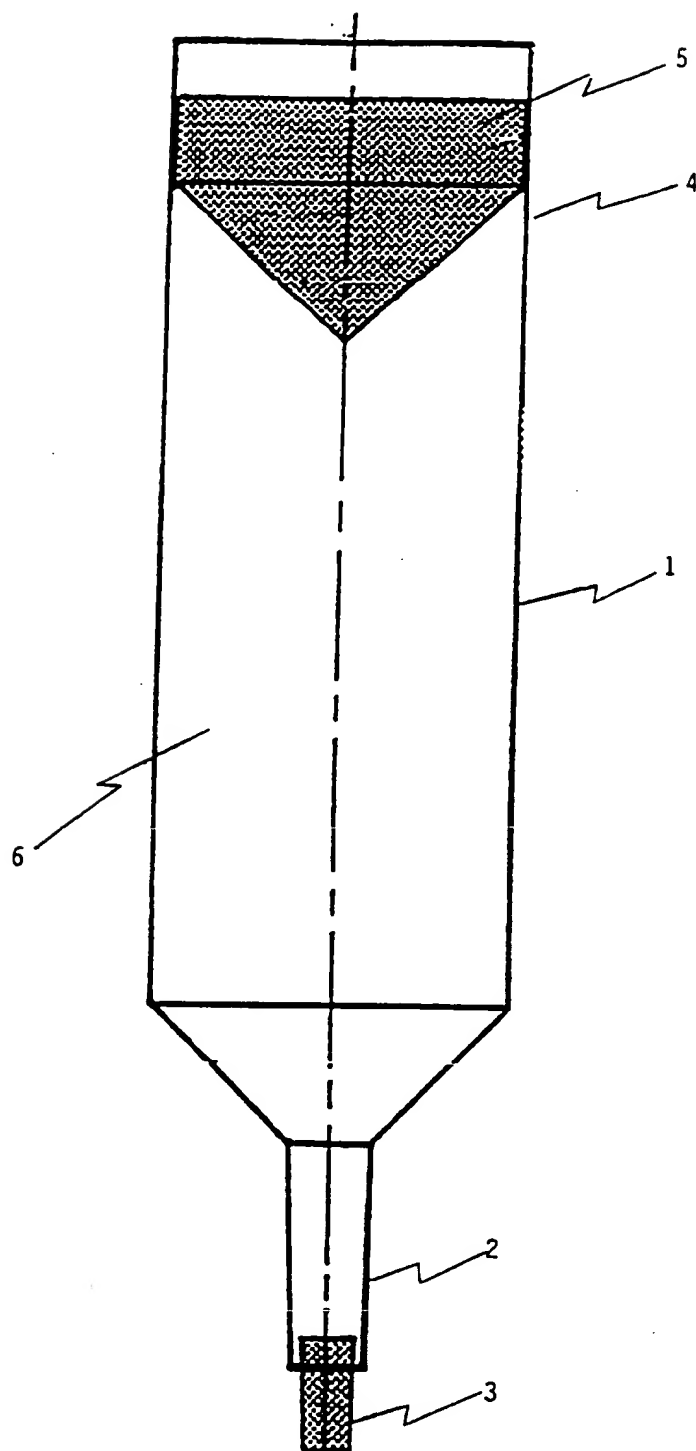


FIGURE 1

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/IB 94/00327

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B29C45/17 B29C67/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B29C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUROPEAN PLASTICS NEWS, vol.18, no.8, October 1991 pages 24 - 25 COOKE F. 'Getting started in medical plastics' see page 24, left column, line 28 - line 52 ---	1-16
X	PLASTICS SOUTHERN AFRICA, vol.21, no.4, September 1991 page 10 'Disposable syringes: Klöckner standards for mass production' see page 10, left column, line 13 - line 18 --- -/--	1-16

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

9 February 1995

Date of mailing of the international search report

22-02-1995

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INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/IB 94/00327

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTEC 91- CONFERENCE PROCEEDINGS, May 1991 pages 412 - 416 GALIC G. ET AL. 'Molded parts discharged without opening the mold' see page 413, right column, line 69 - page 414, left column, line 21 ---	1-16
A	DATABASE RAPRA RAPRA TECHNOLOGY LTD., SHAWBURY, SHREWSBURY, SHROPSHIRE, GB AN : 489025 KIRKLAND C. 'Safer syringes boost moulder opportunities' see abstract & PLASTICS WORLD, vol.51, no.8, August 1993 pages 20 - 24 ---	1-16
A	KUNSTSTOFFE, vol.81, no.9, September 1991, MÜNCHEN pages 768 - 770 ECKARDT H. 'Spritzgiessen im Reinraum' see page 768, left column, line 1 - line 12 see page 768, right column, line 38 - page 769, left column, line 5 ---	1-16
A	US,A,4 718 463 (JURGENS JR. ET AL.) 12 January 1988 cited in the application see column 1, line 42 - column 2, line 15 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 94/00327

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